Pelvic Organ Prolapse

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CHAPTER 5

EFFECTIVENESS AND COST-EFFECTIVENESS OF PESSARY TREATMENT COMPARED WITH PELVIC FLOOR MUSCLE TRAINING IN OLDER WOMEN WITH PELVIC ORGAN PROLAPSE: 2-YEAR FOLLOW-UP OF A RANDOMIZED CONTROLLED TRIAL IN PRIMARY CARE

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ABSTRACT

Objective

We investigated the effectiveness and cost-effectiveness of pessary treatment compared with PFMT in women with prolapse over a 2-year period.

Methods

Randomized controlled trial with women (55 years and older) with symptomatic prolapse, identified by screening. Participants were recruited from 20 primary care practices (October 2009-December 2012). Primary outcome was the difference in change of pelvic floor symptoms (PFDI-20 score) between groups over 24 months. Secondary outcomes included prolapse, urinary, and anorectal symptoms; quality of life; costs; sexual functioning; prolapse stage; pelvic floor muscle function; and participants' perceived symptom improvement.

Results

There was a nonsignificant difference in the primary outcome between pessary treatment (n = 82) and PFMT (n = 80) with a mean difference of -3.7 points (95% CI -12.8 to 5.3; p = 0.42) in favor of pessary treatment. A significantly greater improvement in the prolapse symptom score was, however, seen with pessary treatment (mean difference -3.2 points [95% CI -6.3 to -0.0; p = 0.047]). Direct medical costs over the 2-year study were $309 and $437 per person for pessary treatment and PFMT, respectively.

Conclusions

In older women with symptomatic prolapse, there was no significant difference between pessary treatment and PFMT in reducing pelvic floor symptoms, but specific prolapse-related symptoms did improve more with pessary treatment. Pessary treatment was preferable in the cost-effectiveness analysis. When counseling women for prolapse treatment it should, however, be taken into account that pessary fitting fails in a considerable portion of women and that pessary treatment was associated with more side effects compared with PFMT.

INTRODUCTION

Prolapse is characterized by descent of the vaginal walls, uterus, or vaginal vault.[1] It is a common condition, and in a Dutch population survey of women aged 45 to 85 years, 39% had moderate to severe prolapse on physical examination.[2] Given that the average age of the population is increasing, and given that the incidence of prolapse increases with age,[3] the prevalence of prolapse is expected to increase. Women with a prolapse can present with a variety of pelvic floor symptoms, including vaginal bulging, pelvic pressure or heaviness, pelvic pain, and urinary or fecal incontinence or obstruction.[4] Prolapse can, therefore, lead to discomfort and can negatively influence daily activities, sexuality,[5] and quality of life.[6] Treatment options for prolapse include vaginal pessaries, PFMT, and surgery. The lifetime risk for prolapse surgery varies between 6% and 19%,[7] and the monetary costs are expected to increase substantially in Western societies because of the aging population.[7,8] This is a significant issue, and further efforts are needed to provide cost-effective nonsurgical treatment options.
Pessaries are considered a first-line treatment for prolapse in the United States, being used by 77% of gynecologists.[9] This practice is supported by observational studies that have consistently shown pessaries to be effective in improving prolapse-related pelvic floor symptoms.[10-14] PFMT also seems to be effective in improving prolapse-related pelvic floor symptoms when compared with no treatment.[15-22] In a Cochrane review, Bugge et al.[23] emphasized that there is an urgent need for randomized studies to compare the use of pessaries with other conservative measures. To date, though, pessary treatment and PFMT have not been directly compared and there is only limited information on the monetary costs of these conservative treatments. Therefore, in this 2-year follow-up study, we aimed to compare the effectiveness, defined as improvement of pelvic floor symptoms, and the cost-effectiveness of pessary treatment and PFMT in a primary care population of women aged at least 55 years with a symptomatic prolapse at or beyond the hymen.

METHODS

Design and setting

This was a randomized controlled trial performed in 20 primary care practices in the Netherlands. Participants were enrolled between October 14, 2009 and December 15, 2012. The last date of follow-up was December 10, 2014. The study design has previously been published.[24] The trial was registered in the Dutch Trial Register and was approved by the Medical Ethics Committee of the University Medical Centre Groningen. All participants gave written informed consent.

Participants

Participating primary care physicians included all women aged at least 55 years registered in their practice. Women were excluded if they had undergone prolapse treatment in the previous year, were currently undergoing treatment for another urogynecological disorder, had a pelvic organ malignancy, or had impaired mobility, severe or terminal illness, cognitive impairment, or insufficient Dutch language comprehension. Eligible women then received a 5-item screening questionnaire by post.[24] This included questions on pelvic floor symptoms possibly related to prolapse (urinary incontinence, vaginal bulging, pelvic heaviness/pressure, and the need for vaginal splinting to start or complete micturition or defecation). Women who screened positive for one or more of these symptoms were invited for a baseline assessment.
The baseline assessment involved participants completing a set of questionnaires and undergoing a standardized interview and physical examination conducted by a research physician. The degree of prolapse was measured during the physical examination using the POP-Q system.[25] Women in whom the leading edge of the prolapse was at or beyond the hymenal remnants (POP-Q advanced stage 2 or stage 3) were considered to have an advanced prolapse andwere eligible for the trial. Women with stage 4 prolapse were advised to consult their physician to get further information about the available treatment options.

Randomization and blinding

Eligible women were randomly allocated to pessary treatment or PFMT in a 1:1 ratio using an external computer system with an interactive voice response system (accessible by telephone). Block randomization with variable block sizes was used. Four research physicians were involved in this study. The research physician enrolling participants was blinded to the allocation sequence, the ordering of the blocks, and the size of the blocks. It was not possible to blind participants or physiotherapists to the treatment because of the nature of the intervention. Equally, it was not feasible to blind the research physicians to group allocation because of their roles in treatment evaluation (eg, for the side effects of pessary treatment) and follow-up assessment. Research physicians performing the follow-up assessment were, however, blinded to all answers on the participant-completed questionnaires and to the outcomes of previous POP-Q measurements and evaluations of pelvic floor muscle function. Pelvic physiotherapists were also blinded to the answers on the participant-completed questionnaires. Data analysts were blinded to group allocation.

Interventions

Pessary treatment

Pessaries were fitted by a trained research physician. The first choice was an open ring

pessary, followed by a ring pessary with support. If a ring pessary could not be fitted, a Shaatz or Gellhorn pessary was tried. All pessaries were made of silicone (Milex, Chicago, IL). A pessary was considered to have the correct size when the physician could place a finger between the pessary and the vaginal wall, the prolapse was reduced to above the hymen, it felt comfortable to the participant, and was retained during a Valsalva maneuver and coughing in both supine and standing positions. Pessary treatment was evaluated after 2 weeks. Pessary fitting was regarded as successful when participants had used the pessary without discomfort for 2 weeks. Participants in whom the pessary fell out or who experienced discomfort within the first 2 weeks were refitted with a different type or size of pessary and reviewed again after another 2 weeks. This procedure was repeated up to a maximum of three attempts. If a pessary was not fitted successfully after three attempts, pessary fitting was regarded as unsuccessful.

An experienced urogynecologist trained the four research physicians in pessary fitting and this urogynecologist was also available for consultation when difficulties were encountered during the fitting process. Additional control visits were scheduled every 3 months to clean the pessary, evaluate treatment, and monitor side effects by the participant's own general practitioner, or by one of the research physicians, depending on the choice of the general practitioner and the participant. In some cases, the physician who performed the outcome assessment was also the physician who had done the regular pessary checks. When a pessary led to vaginal discharge, irritation, or erosions, women were advised not to wear the pessary for 2 weeks and were reviewed again. Topical estrogen was suggested in cases of discharge or ulceration due to vaginal atrophy.

Pelvic floor muscle training

Women randomized to PFMT were referred to a pelvic physiotherapist and their treatment started with an explanation of the function of the pelvic floor. Their pelvic floor muscle function and the ability to contract and relax the pelvic floor muscles correctly was examined using digital palpation. Women who were unable to contract or relax their pelvic floor muscles were first instructed how to do this. They received feedback during digital palpation or, if necessary, by applying myofeedback or electrical stimulation. As soon as they were able to control their pelvic floor they started the training by doing exercises during face-to-face contact and at home (3-5 times a week, 2 or 3 times each day). All participants started with the same exercise regime, which was later tailored to the needs of each participant by adding specific exercises based on findings during the pelvic floor examination (Appendix I). In women with an overactive pelvic floor, relaxation exercises were used and the focus of the exercises

was on relaxation rather than contraction. All participants were taught ''the knack,'' meaning that they learned to contract their pelvic floor muscles before and during any increase in abdominal pressure. Furthermore, attention was paid to toilet habits and lifestyle (eg, diet, smoking, and body weight) (Appendix I). Treatment modalities and the number of sessions were recorded for each participant. To minimize the effect of differences in experience or skill, all participating pelvic physiotherapists were required to be registered with the Dutch Pelvic Physiotherapists' Organization.

Follow-up

Follow-up appointments were scheduled 3, 12, and 24 months after the start of PFMT or after reaching a successful pessary fitting. Follow-up included questionnaires and an examination of the pelvic floor, including a POP-Q measurement and an assessment of pelvic floor muscle function. Women wearing a pessary were asked to remove their pessary (or have it removed by their general practitioner) 24 to 48 hours before the follow-up assessments. Women in whom pessary fitting was unsuccessful were followed up by questionnaire through the 24-month period. Participants who were not able to attend the follow-up appointment were also asked to complete follow-up questionnaires sent by post. In addition, nonattenders were phoned to check whether they had received consultations or treatments for prolapse symptoms and to check their use of absorbent pads. All women were allowed to consult their physician for symptoms of prolapse during the study period. Women were asked about these consultations and treatments at follow-up and the details recorded.

Outcome measures

Primary outcome

The primary outcome was distress caused by pelvic floor symptoms, as measured with the PFDI-20.[26] This is a validated, participant-completed questionnaire with 20 questions about prolapse, anorectal, and urinary symptoms.[27] The PFDI-20 score ranges from 0 to 300, with higher scores indicating higher distress from pelvic floor symptoms.

Secondary outcomes

Secondary outcomes were the three subscales of the PFDI-20, which measure the distress caused by prolapse symptoms (POPDI-6), anorectal symptoms (CRADI-8), and urinary symptoms (UDI-6). Condition-specific and general quality of life were assessed with the Pelvic Floor Impact Questionnaire-7 (PFIQ-7)[26] and by the physical (PCS-12) and mental (MCS-12) component scores of the MOS-SF-12, respectively.[28] Sexual functioning was measured with the PISQ-12.[29] At 24 months, a five-point

scale was used to assess participants' perceived global perception of improvement from the start of the study (much better, better, the same, worse, or much worse).[30] Costs were measured at each follow-up using a questionnaire based on the Medical Consumption Questionnaire (iMCQ).[31] Adaptations were made to the selection of relevant cost items, such as the details of consultations, prolapse-related treatments, and the use of absorbent pads. The three-level version of the EuroQol health status measure (EuroQol 5D-3L) was used to collect data for the cost-utility analysis.[32] Data on adverse treatment effects were collected during follow-up assessments.
The degree of prolapse was assessed with the POP-Q system.[25] In the POP-Q system, the degree of prolapse of the anterior vaginal wall (point Ba), the posterior vaginal wall (point Bp), and the uterus (or vaginal vault in case of hysterectomy) (point C) is measured in centimeters relative to the hymenal remnants. These measurements are converted to an ordinal scale of four prolapse stages for each compartment (anterior, posterior, apical). The overall POP-Q stage is equal to the POP-Q stage of the most severely prolapsed compartment. Pelvic floor muscle function was assessed by digital vaginal palpation in the supine position and was categorized as normal, underactive, overactive, or inactive according to the International Continence Society classification.[33] Research physicians were trained to perform a POP-Q measurement and to evaluate the pelvic floor muscles by an experienced urogynecologist.

Statistical analyses

Based on an estimated clinically relevant difference in change of the PFDI-20 score of 20 points between groups, and a standard deviation of 36 points,[34] for a type I error of 5%, power of 80%, successful pessary fitting in 70%, and dropout rate of 15% after 2 years, we needed to enroll 148 women.[24] All statistical tests were performed two-sided at a 5% significance level.

Primary and secondary outcomes

Outcome variables were repeatedly measured over time and compared between groups, so the statistical approach needed to correct for the correlated longitudinal information. Therefore we used MLwiN 2.29 (Centre for Multilevel Modeling, University of Bristol, UK) to conduct a multilevel analysis. Multilevel models produce hierarchical models that estimate regression coefficients and related variance components while correcting for the dependency of information. The lower level was defined as time of measurement and the upper level as the participant. The restricted iterative generalized least squares algorithm was used to estimate the regression coefficients, whereas the Wald test was used to obtain a *p*-value for each regression coefficient. Linear multilevel analysis that included a fixed and random intercept[35] was conducted

to test the longitudinal difference between treatment groups with respect to the primary outcome variable (ie, PFDI-20) and the secondary outcome variables (ie, POPDI-6, CRADI-8, UDI-6, PFIQ-7, PCS-12, MCS-12, and PISQ-12). For each equation, two primary intention-to-treat (ITT) analyses and two secondary per-protocol (PP) analyses were conducted, each with and without adjusting for the questionnaire and POP-Q (stage 2 or stage 3) baseline scores. The ITT population we used included all women randomized to each treatment arm, whereas the PP population only included those who completed the intervention to which they were allocated. Participants were excluded from the PP analyses if pessary fitting was unsuccessful, if they discontinued pessary treatment, if they did not start PFMT, and if they discontinued PFMT prematurely (according to the records of the pelvic physiotherapist).

Additional analyses were performed, based on the PP population, to establish the relationship between the degree of prolapse (of the anterior vaginal wall [point Ba], the posterior vaginal wall [point Bp] and the uterus or vaginal vault [point C]) and the treatment group after adjusting for baseline POP-Q measurements. We did not impute missing data because it is considered redundant to replace missing values in longitudinal datasets.[36] Normal probability plots and plots of standardized residual versus predicted values were inspected to assess if they met the assumptions of normality and homogeneity of the variance. In the event of noncompliance, a square root transformation of one of the baseline variables was performed.

Cost-effectiveness analysis

Direct medical costs were calculated for both groups. Cost categories were: pessaries and pessary-related visits, costs for physical therapy, consultations with general practitioners and medical specialists, the use of absorbent pads, medication, and other costs (mainly operative procedures). Costs were first valued in Euros according to Dutch guidelines[37] at the 2014 price level, and later converted to US dollars based on the exchange rate on November 24, 2015 (€1.00 = $1.0657). In the economic evaluation, we compared pessary treatment with PFMT in a cost-effectiveness analysis. Here, we assessed the incremental costs per point improvement on the PFDI-20 and expressed the results as an incremental cost-effectiveness ratio (ICER). In addition, a cost-utility analysis was performed with quality adjusted life years (QALYs) to evaluate the balance between costs and QALYs, by using the EQ-5D-defined utility scores based on the UK tariff.[32] We based our utility scores on the UK tariff for reasons of comparability (eg, the UK tariff is more frequently mentioned than the Dutch tariff in the literature). The outcomes are presented as an incremental cost-utility ratio (ICUR). Costs and effects were recorded and calculated on an individual participant basis, after which the mean differences of effects and costs between the

two treatment groups were calculated. Point estimates of the ICER and ICUR were computed by dividing the difference in effects by the difference in costs between interventions. Bootstrap analyses (5,000 replications of the trial data) were performed to estimate alternative confidence intervals based on the 2.5th and 97.5th percentiles. Cost-effectiveness planes were constructed to visualize the uncertainty surrounding the ICER and ICUR.

RESULTS

Participants and descriptive statistics

In total, 162 women were randomized to pessary treatment (n = 82) or PFMT (n = 80) (Figure 1). Table 1 shows the baseline characteristics of the study population.

The pessary group

Pessary fitting was successful in 47 women (57%); of these, 32 were fitted with an open ring pessary, 14 with a ring pessary with support, and 1 with a Shaatz pessary. During the study period, the pessary was replaced by another type and/or size in 12 women. A total of 35 women did not receive pessary treatment, mostly due to unsuccessful fitting (n = 34). In one participant, no fitting attempt was made since she seemed to meet one of the study's exclusion criteria (cognitive impairment). In 21 of the 34 women with unsuccessful fitting (62%), no suitable pessary could be found. Other reasons for deciding against pessary treatment during the fitting period were an increase in or development of urinary incontinence (n = 4), emotional resistance to pessary fitting/treatment (n = 5), discomfort during intercourse (n = 2), and a bothersome increase in vaginal discharge (n = 1; the participant was not willing to use topical estrogens). One woman (n = 1) reported a urinary tract infection during the fitting period and chose to discontinue the pessary treatment.

Baseline characteristics did not differ between women with and without a successful pessary fitting (data not shown). The median number of consultations for women with successful pessary fitting was 1.0 (IQR 1.0-2.0), and that for women with unsuccessful fitting was 2.0 (IQR 2.0-3.0). Of the 47 women who started pessary treatment, 12 discontinued the treatment before the end of the study (Figure 1). During the study, seven women in the pessary group received PFMT for prolapse symptoms (after unsuccessful pessary fitting) and four women underwent prolapse repair surgery (pessary fitting was only successful in one).

The pelvic floor muscle training group

Of the 80 women randomized to PFMT, four did not attend pelvic physiotherapy and

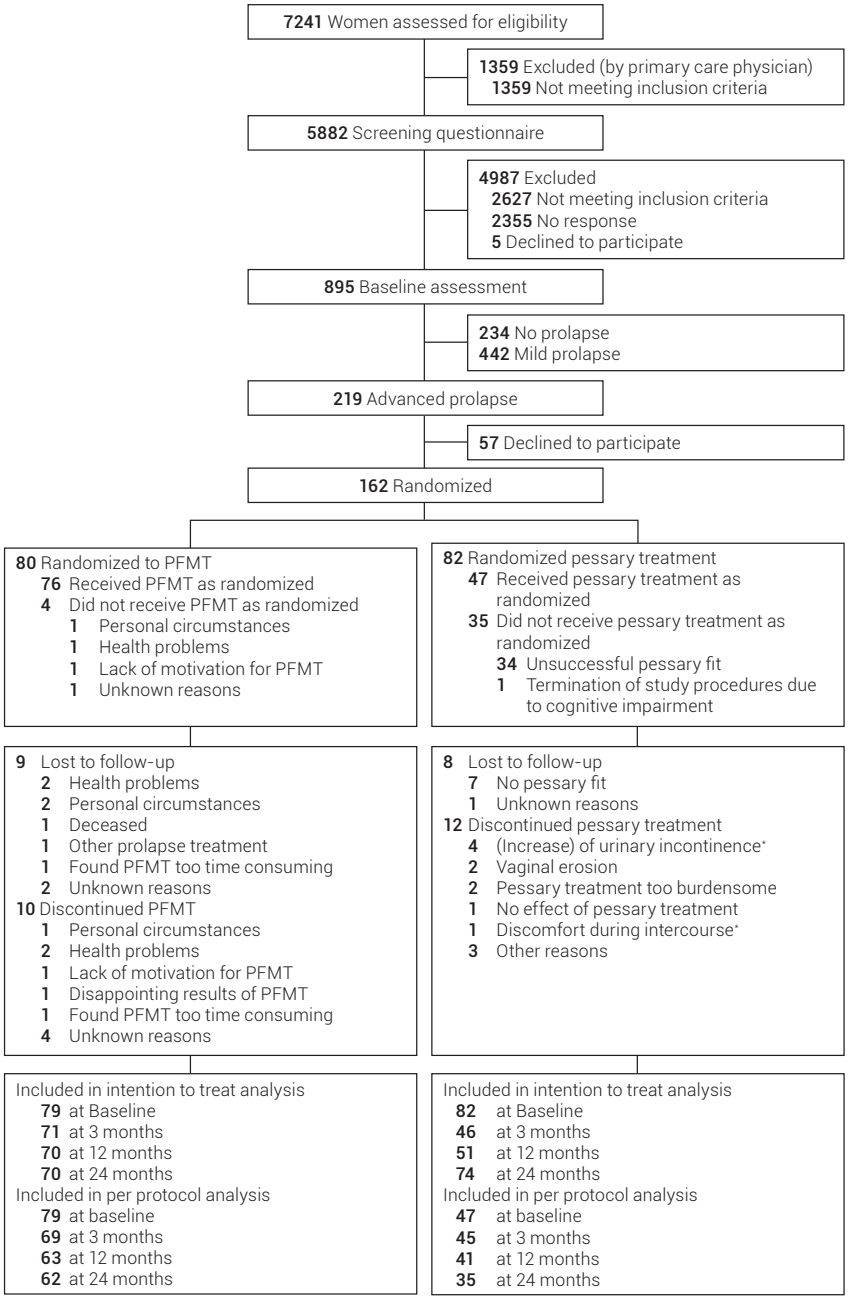

FIGURE 1 FLOWCHART OF PARTICIPANTS THROUGH STUDY

*One women had both urinary incontinence and discomfort during intercourse.

TABLE 1 BASELINE CHARACTERISTICS

	PFMT n = 80	Pessary n = 82
Age (years), mean ± SD	65.6 ± 6.4	64.9 ± 7.4
BMI (kg/m^2), mean ± SD	26.6 ± 4.3	26.1 ± 3.8
Parity, mean ± SD	2.6 ± 1.1	2.4 ± 0.9
Postmenopausal, n (%)	80 (100)	81 (99)
Educational level, n (%)		
Primary only	6 (8)	3 (4)
Lower	26 (33)	31 (38)
Intermediate	25 (31)	22 (27)
Higher	23 (29)	26 (32)
Surgical history, n (%)		
Hysterectomy	10 (13)	15 (18)
Pelvic floor surgery	7 (9)	8 (10)
Prior prolapse treatment, n (%)*	21 (26)	18 (22)
Stage of prolapse, n (%)†		
Stage 2	62 (78)	58 (71)
Stage 3	18 (23)	24 (29)
Type of prolapse, n (%)		
Anterior	25 (31)	20 (25)
Posterior	3 (4)	0 (0)
Apical	0 (0)	0 (0)
Anterior and posterior	26 (33)	23 (28)
Anterior and apical	8 (10)	19 (24)
Posterior and apical	2 (3)	0 (0)
Anterior and posterior and apical	16 (20)	19 (24)

*Surgical or conservative prolapse treatment >1 year ago; †POP-Q stage of most prolapsed compartment

10 discontinued PFMT prematurely (Figure 1). One woman was erroneously included in the PFMT group (she had a prolapse but no symptoms on screening) and was therefore excluded from the analyses. For participants who completed PFMT, the median number of treatments was 7 (IQR 6-10). PFMT was given over a median timeframe of 16 weeks (IQR 12-30 weeks). Myofeedback was used in 14 participants (22%) and electric stimulation in nine (14%). During the study period, three women in the PFMT group received pessary treatment for prolapse symptoms and two women underwent surgery for prolapse.

TABLE 2 QUESTIONNAIRE BASELINE AND FOLLOW-UP SCORES (INTENTION TO TREAT)*

	PFMT								Pessary							
	Baseline		3 months		12 months		24 months		Baseline		3 months		12 months		24 months	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
PFDI-20	75	65.0 ± 35.8	69	55.8 ± 37.4	66	60.2 ± 40.9	67	62.6 ± 43.8	79	59.8 ± 33.7	43	50.1 ± 30.6	45	50.6 ± 35.9	71	50.5 ± 34.7
POPDI-6	78	16.9 ± 13.0	70	15.6 ± 13.6	69	16.4 ± 15.4	68	17.1 ± 15.9	81	17.4 ± 13.5	45	13.2 ± 12.5	48	12.8 ± 12.8	73	12.9 ± 13.1
CRADI-8	75	18.1 ± 15.0	70	16.8 ± 16.4	66	17.7 ± 15.5	69	18.1 ± 16.0	81	15.7 ± 13.8	43	12.4 ± 10.5	48	14.2 ± 12.3	72	13.6 ± 13.4
UDI-6	76	30.4 ± 17.0	70	23.3 ± 16.6	68	25.0 ± 18.5	68	26.6 ± 20.6	81	27.2 ± 17.5	44	23.7 ± 16.3	47	22.3 ± 17.9	72	24.4 ± 16.0
PFIQ-7	74	19.4 ± 25.9	65	15.3 ± 20.1	66	15.8 ± 26.0	66	19.0 ± 28.5	79	18.5 ± 28.2	41	13.1 ± 26.1	50	19.1 ± 36.9	67	16.0 ± 28.7
PISQ-12†	29	37.4 ± 4.1	25	37.7 ± 4.7	24	37.6 ± 4.2	24	36.7 ± 4.5	41	35.5 ± 5.1	19	37.7 ± 4.5	24	35.3 ± 5.9	34	35.7 ± 5.1
PCS-12	70	46.9 ± 11.4	64	46.4 ± 10.0	65	46.0 ± 10.4	60	44.9 ± 10.4	73	45.4 ± 9.9	44	46.7 ± 9.5	43	47.2 ± 8.8	70	47.2 ± 8.6
MCS-12	70	51.9 ± 8.9	64	52.3 ± 8.7	65	53.5 ± 8.3	60	53.9 ± 7.9	73	52.2 ± 10.1	44	52.1 ± 10.4	43	51.6 ± 10.3	70	52.2 ± 9.4

*This table shows the number of questionnaires which were sufficiently completed to calculate a score; †Only available for sexually active women

TABLE 3 DIFFERENCE IN QUESTIONNAIRES BETWEEN PFMT AND PESSARY TREATMENT OVER THE COURSE OF 24 MONTHS

		Intention to treat		Per protocol	
		Mean (95% CI)	*p*-value	Mean (95% CI)	*p*-value
PFDI-20		-8.5 (-20.0 to 3.0)	0.15	-14.1 (-29.0 to 0.8)	0.064
	Adjusted*	-3.7 (-12.8 to 5.3)	0.42	-5.7 (-17.4 to 6.1)	0.35
POPDI-6		-3.8 (-8.0 to 0.4)	0.079	-5.6 (-11.1 to -0.1)	0.046
	Adjusted*	-3.2 (-6.3 to -0.0)	0.047	-4.6 (-8.6 to -0.6)	0.024
CRADI-8		-3.9 (-8.2 to 0.4)	0.075	-5.1 (-10.9 to 0.7)	0.087
	Adjusted*	-2.0 (-5.3 to 1.2)	0.22	-2.0 (-6.0 to 2.0)	0.33
UDI-6		-0.7 (-6.0 to 4.6)	0.80	-3.8 (-10.4 to 2.8)	0.26
	Adjusted*	1.1 (-3.3 to 5.5)	0.63	-0.4 (-5.8 to 5.1)	0.90
PFIQ-7†		-2.2 (-11.1 to 6.7)	0.63	-7.3 (-18.2 to 3.5)	0.19
	Adjusted*	1.2 (-5.3 to 7.7)	0.72	1.1 (-6.2 to 8.4)	0.77
PISQ-12‡		-1.5 (-3.8 to 0.8)	0.20	0.0 (-2.9 to 2.9)	0.99
	Adjusted*	0.2 (-1.2 to 1.5)	0.83	1.2 (0.1 to 2.2)	0.028
PCS-12		1.2 (-1.7 to 4.1)	0.43	2.9 (-0.9 to 6.8)	0.13
	Adjusted*	2.1 (0.0 to 4.1)	0.050	3.7 (1.2 to 6.2)	0.004
MCS-12		-1.0 (-3.8 to 1.7)	0.46	-1.6 (-5.3 to 2.2)	0.41
	Adjusted*	-1.2 (-3.3 to 0.8)	0.24	-1.7 (-4.1 to 0.7)	0.17

*Adjusted for baseline score and baseline POP-Q stage (2 or 3); †PFIQ-7 baseline score square root transformation; ‡Only available for sexually active women

Questionnaire scores

The questionnaire scores are summarized in Table 2. For the primary outcome (total PFDI-20 score), there was no significant difference in the longitudinal analyses between pessary treatment and PFMT: the ITT analysis showed a difference of -3.7 points (95% CI -12.8 to 5.3; p = 0.42), whereas the PP analysis showed a slightly greater difference of -5.7 points (95% CI -17.4 to 6.1; p = 0.35) both in favor of the pessary group (Table 3).

It is notable that there was a difference between groups in the evolution of PFDI-20 scores during the 24 months. Both groups showed an improvement in pelvic floor symptoms, as can be seen by the decrease in the PFDI-20 scores from baseline to follow-up at 3 months. In the following period (from 3 months to the end of the study), the mean PFDI-20 score in the PFMT group slowly increased again, with scores at the end of the study being almost equal to the baseline scores (ie, there was a 2.8-point (4%) difference between baseline and 24 months). In contrast, the improvement in pelvic floor symptoms in the pessary group continued until the end of the study, with

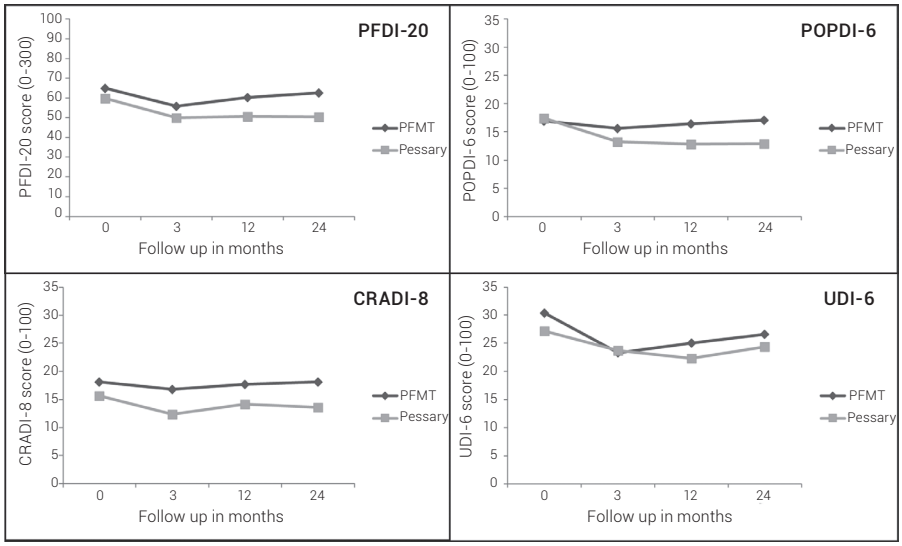

FIGURE 2. COURSES OF THE TOTAL PFDI-20 AND THE PFDI-20 SUBSCALE SCORES DURING THE STUDY

a 9.3-point (16%) difference between baseline and 24 months (Figure 2).

The ITT analyses showed a significant difference in prolapse (POPDI-6) symptoms between groups in favor of the pessary group over the 24 months (mean difference -3.2 points [95% CI -6.3 to -0.0, p = 0.047]) (Table 3). In the pessary group, the POPDI-6 score improved by 4.2 points (24%) between baseline and 3 months, and the improvement remained until the end of the study. In the PFMT group, prolapse symptoms improved slightly between baseline and 3 months, but the POPDI-6 score had almost reached the baseline score again by 24 months (Table 2) (Figure 2). There were no significant differences between groups for the other secondary questionnaire outcomes.

The PP analyses showed a significant difference between groups in favor of the pessary group for sexual functioning (PISQ-12) and in favor of the PFMT group for the physical component of general quality of life (PCS-12) (Table 3). After 24 months, the proportion of women who reported that their symptoms were improved, the same, or worse was comparable between the two groups (Table 4).

Physical examination

During the 24 months, there was a difference between the groups in the change in degree of prolapse of the anterior compartment (point Ba 0.42 [95% CI 0.01 to 0.83, p =

TABLE 4 SELF-REPORTED CHANGE OF SYMPTOMS FROM THE START OF THE STUDY

	Intention to Treat			Per Protocol		
	PFMT n/N (%)	Pessary n/N (%)	*p*-value*	PFMT[a] n/N (%)	Pessary n/N (%)	*p*-value*
Much better	6/70 (9)	6/72 (8)		4/57 (7)	4/35 (11)	
Better	18/70 (26)	19/72 (26)		15/57 (26)	11/35 (31)	
The same	35/70 (50)	41/72 (57)	0.45	29/57 (51)	17/35 (49)	0.67
Worse	11/70 (16)	5/72 (7)		9/57 (16)	3/35 (9)	
Much worse	0/70 (0)	1/72 (1)		0/57 (0)	0/35 (0)	

*Chi-square test

TABLE 5 CHANGE OF POP-Q STAGE BETWEEN BASELINE AND 24 MONTHS

	Intention to Treat			Per Protocol		
	PFMT n/N (%)	Pessary n/N (%)	*p*-value*	PFMT n/N (%)	Pessary n/N (%)	*p*-value*
Improvement†	9/62 (15)	9/43 (21)		8/52 (15)	6/35 (17)	
The same	43/62(69)	28/43 (65)	0.69	36/52 (69)	25/35 (71)	0.86
Deterioration‡	10/62 (16)	6/43 (14)		8/52 (15)	4/35 (11)	

*Chi-square test; †Improvement ≥1 POP-Q stage; ‡Deterioration ≥1 POP-Q stage

0.04]) in favor of the PFMT group. This was, however, not the case for either the apical segment (point C -0.06 [95% CI -0.45 to 0.34, p = 0.78]) or the posterior compartment (point Bp 0.19 [95% CI -0.07 to 0.45, p = 0.14]) (PP analysis only).

The proportion of women with improvement or deterioration of at least one POP-Q stage, or in whom the POP-Q stage remained the same between baseline and 24 months, did not differ between groups (Table 5). The change in pelvic floor muscle function between baseline and 24 months was also comparable in both groups (Table 6).

Adverse events

Of the 35 women who persisted with pessary treatment for 24 months, 21 (60%) had one or more side effects. These were increased vaginal discharge (n = 14), an increase of urinary incontinence (n = 5), and irritation or erosions of the vaginal walls on physical examination (n = 10). Women with mild irritation of the vaginal walls were advised to not wear the pessary for 2 weeks in the first instance, but 7 of 10 women

TABLE 6 CHANGE OF PELVIC FLOOR MUSCLE FUNCTION BETWEEN BASELINE AND 24 MONTHS

	Intention to Treat			Per Protocol		
	PFMT n/N (%)	Pessary n/N (%)	*p*-value*	PFMT n/N (%)	Pessary n/N (%)	*p*-value*
Abnormal>Normal						
Underactive>Normal	13/62 (21)	13/43 (30)		10/52 (19)	13/35 (37)	
Overactive>Normal	0/62 (0)	0/43 (0)		0/52 (0)	0/35 (0)	
The same	41/62 (66)	29/43 (67)		36/52 (69)	22/35 (63)	
Normal>abnormal			0.21			0.08
Normal>Underactive	3/62 (5)	1/43 (2)		2/52 (4)	0/35 (0)	
Normal>Overactive	1/62 (2)	0/43 (0)		1/52 (2)	0/35 (0)	
Abnormal>Abnormal						
Underactive>Overactive	2/62 (3)	0/43 (0)		2/52 (4)	0/35 (0)	
Overactive>Underactive	2/62 (3)	0/43 (0)		1/52 (2)	0/35 (0)	

*Chi-square test

with irritation or erosions of the vaginal walls were prescribed topical estrogen. No adverse effects were reported for PFMT.

Cost-effectiveness

Direct medical costs over the 2-year study, per person, amounted to $309 in the pessary group and $437 in the PFMT group. The mean difference was $128 (95% CI $27 to $236), with costs dependent on the primary treatment. Costs for pessaries and pessary-related visits were higher in the pessary group ($202 per person compared with $0.5 in the PFMT group), whereas costs for physical therapy were higher in the PFMT group ($324 per person for the PFMT group compared with $2 in the pessary group). Although costs for visits to the general practitioner and medical specialist were comparable in both groups ($32 per person in the pessary group compared with $35 in the PFMT group), costs for absorbent pads, however, were higher in the PFMT group ($56 per person compared with $20 in the pessary group) and costs for other prolapse treatments (ie, surgery) were higher in the pessary group ($44 per person compared with $22 in the PFMT group).

The ICER for the PFDI-20 was -$77 (95% CI -$373 to $351), meaning that $77 was preserved to improve one additional point on the PFDI-20 in the pessary group compared with the PFMT group. In total, 71% of the 5,000 replications in the bootstrap simulation were in the southeast quadrant of the cost-effectiveness plane, indicating better outcomes and lower costs for the pessary group (Figure 3). The remaining 29% were located in the southwest quadrant, indicating less effectiveness and lower costs for the pessary group over the PFMT group.

Both treatment groups lost QALYs over the 2-year period, although loss of QALYs was slightly lower in the pessary group (0.024 in the pessary group and 0.065 in the PFMT group). This resulted in a negative ICUR of -$27,439 (95% CI -$91,974 to $74,695), meaning an additional saving of $27,439 per QALY lost. Of the 5,000 bootstrap replications, 95% were located in the southeast quadrant of the costeffectiveness plane, indicating greater effect and lower costs. The remaining 5% were located in the southwest quadrant, indicating less effect and lower costs for the pessary group compared with the PFMT group (Figure 4).

DISCUSSION

Main findings

During the 24-month study period, we found no difference in the change in pelvic floor symptoms between pessary treatment and PFMT in women aged 55 years or older recruited by screening. Although pessary treatment led to a statistically significant

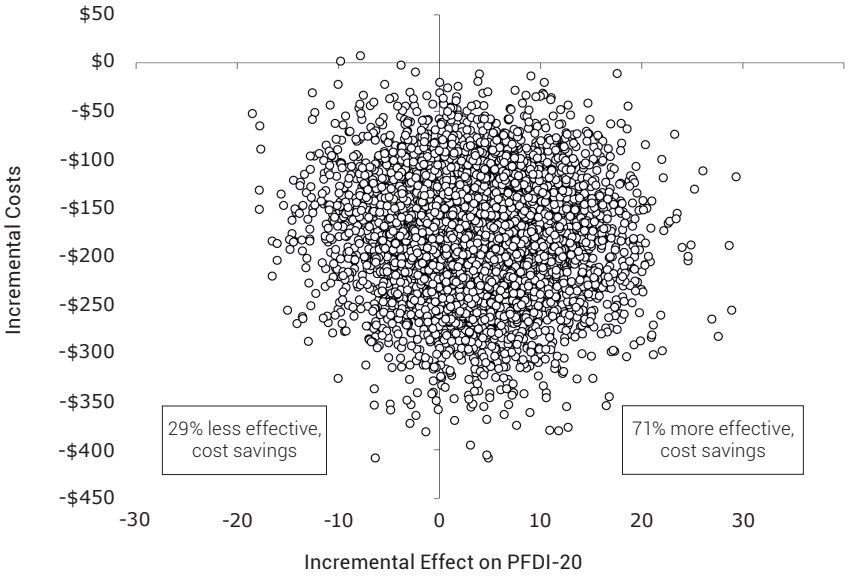

FIGURE 3. INCREMENTAL COST-EFFECTIVENESS PLANE FOR THE PFDI-20

5000 bootstrap replications for the mean difference between costs and PFDI-20.

greater improvement in typical prolapse symptoms compared with PFMT, the difference was small and the clinical relevance doubtful. Moreover, pessary treatment was less expensive than PFMT, as indicated by the direct medical costs of $309 per person in the pessary group and $437 per person in the PFMT group over the 2-year period.

Strengths and limitations

The strengths of this study are its long follow-up and the focus on participant-reported outcomes. Nevertheless, a number of limitations deserve attention. First, the effects of both treatment options were lower than expected in this study when compared with previous studies on the effects of pessary treatment[10,12,14] and PFMT.[15,16,18,20] There are, however, several possible explanations for this difference.

In the design phase, we decided to screen women for symptomatic prolapse on the assumption that women with prolapse-related symptoms do not necessarily consult a physician.[38] Because all women agreed to participate in one of two active treatment arms, we assumed that the women recruited by screening would be comparable with those seeking treatment for prolapse in primary care (ie, that their PFDI-20 scores

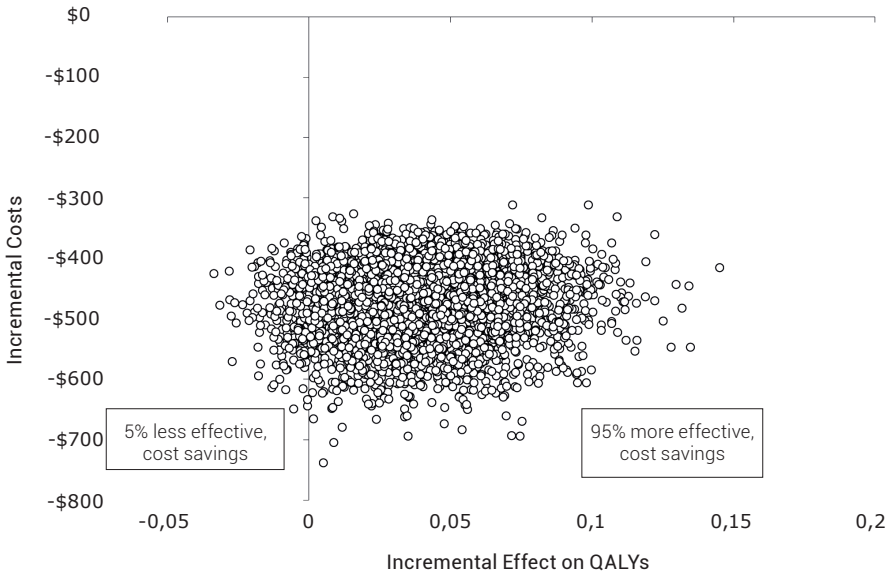

FIGURE 4. INCREMENTAL COST-EFFECTIVENESS PLANE FOR QALYS

5000 bootstrap replications for the mean difference between costs and QALYs.

would be higher). Several women, however, experienced mild distressing pelvic floor symptoms at inclusion, as illustrated by their mean PFDI-20 baseline score of 60 points, which was lower than the expected 80 points suggested by previous research.[39] This might have caused an underestimation of the effectiveness of both pessary treatment and PFMT because the lower baseline scores may have allowed less room for improvement.

Second, women with unsuccessful pessary fitting were followed up by questionnaires only. Because this would bias the results of an ITT analysis for the outcomes ''change of the degree of prolapse'' and ''change of pelvic floor muscle function,'' these secondary outcomes were only analyzed using PP analyses. Consequently, we can only draw conclusions on the difference in change of prolapse stage and pelvic floor muscle function in women who completed pessary treatment or PFMT. Unsuccessful pessary fitting is a known disadvantage of pessary treatment in some women. The results of the PP analyses reflect the effects of actual pessary treatment in women with successful pessary fitting; therefore, these results should be more relevant to clinicians than the results of an ITT analysis.

Third, in the design phase of this trial we assumed 74 enrollments in the pessary

group of which 70% had a successful pessary fitting trial. In reality we included 82 women in the pessary group with a success rate of pessary fitting of 57%. Although this percentage corresponds to fitting rates found in other studies, it was lower than we estimated when designing the study. Because of our recruitment strategy (inclusion of all women with prolapse in a participating practice) we randomized more women than planned and this largely compensates for the greater than estimated pessary fitting failure rate. For the ITT analyses (the primary analyses), we reached the required number of women with a successful pessary fit. In longitudinal analyses, it is considered redundant to replace missing values and therefore we did not use multiple imputation techniques. For the per protocol analyses, we calculated that we needed 44 women finishing pessary treatment after 24 months (attrition rate of 15%). Because of the lower than estimated successful fitting rate (57%) and a higher attrition rate of 25% (n = 12), this number turned out to be 35 instead of 44. Therefore, inferences from the results of the per protocol analyses should be interpreted with caution. Another limitation is that blinding of participants was not possible because of the nature of the intervention. In addition, although outcome assessment was mainly through participant-completed questionnaires, thus avoiding assessor bias, questionnaire responses may have been biased by participants' awareness of treatment allocation. Finally, we ensured that the PFMT interventions were tailored to participants' specific needs. Also, to improve the level of standardization, all physiotherapists were required to be registered with the Dutch Pelvic Physiotherapists' Organization (NVFB) and participants were trained according to the same basic exercise guidelines. Despite these efforts, we cannot exclude the possibility of differences in interventions and practices between physiotherapists; nevertheless, this reflects daily practice and should not invalidate our results.

Interpretation

To date, no randomized controlled trials have compared pessary treatment and PFMT. Observational studies have shown pessaries to be effective in improving pelvic floor symptoms related to prolapse,[10-14] whereas randomized controlled trials have shown PFMT to be effective in improving prolapse-related pelvic floor symptoms compared with no treatment.[15-22]

In our study, pessary fitting was successful in 57% of women randomized to pessary treatment, which is consistent with previous reported success rates of 41% to 86%.[13,40-50] This indicates that pessary fitting fails in a considerable portion of women and that pessary treatment might be suitable for many women but not for all women with a symptomatic prolapse.

Our study showed no significant difference in the change of pelvic floor symptoms

measured by the PFDI-20 during the 24-month period when comparing pessary treatment and PFMT; but, women in the pessary group did show a significantly greater reduction in prolapse-specific symptoms (POPDI-6 scale) (ie, vaginal bulging, heaviness, or pressure in pelvic area, and vaginal splinting for micturition or bowel movement) compared with women in the PFMT group. The POPDI-6 score decreased by almost 26% between baseline and 24 months in the group receiving pessary treatment (indicating less distress related to prolapse symptoms), whereas the score increased slightly for women in the PFMT group. This suggests that women with typical prolapse symptoms benefit from pessary treatment more than from PFMT, which is plausible given that pessaries redress prolapse directly. In the PP analysis, we found significant differences between groups in sexual functioning, the physical component of general quality of life, and the degree of prolapse of the anterior compartment over the 24 months. These differences were, however, small and may not be clinically relevant.

In our study, there was a difference in the proportion of side effects. Sixty percent of women in the pessary group reported one or more side effects whereas no adverse advents were reported for PFMT. For the majority of those women in the pessary group, side effects were no reason to discontinue pessary treatment. It is, however, relevant to discuss side effects when counseling women for the most appropriate conservative treatment for prolapse.

Our study was the first to compare the cost-effectiveness of pessary treatment and PFMT. Over the 2-year period, direct medical costs were lower for pessary treatment compared with PFMT, and costs for the use of absorbent pads were also lower for women in the pessary group. To our knowledge, the cost-effectiveness of either pessary treatment or PFMT has only been addressed in 2 other studies. On the one hand, Hullfish et al. studied the cost-effectiveness of pessary treatment, expectant management, and surgical management for apical prolapse (stage 3, after hysterectomy) in the United States using a Markov decision model. They found pessary treatment to be cost effective, achieving 10.4 quality-adjusted months at a cost of $10,000 per participant. Based on their own experience with pessary treatment, the authors estimated the annual costs of pessary treatment to be $1,300, with the addition of another $324 in case of complications due to pessary use.[51] These numbers may be applicable to the US setting, where specialized outpatient clinics provide pessary treatment, but can probably not be generalized to Dutch general practice. Indeed, the direct medical costs of pessary treatment were considerably lower in our study, with mean costs of just $309 per person over the 2-year period.

On the other hand, Hagen et al. studied the cost-effectiveness of PFMT compared with a control intervention over a 12-month period. The mean costs of PFMT

amounted to $405 per person (£268, based on the exchange rate on November 24, 2015).[18] Interestingly, we found that the direct medical costs of PFMT were a little higher ($437 per person), which probably resulted from the higher number of PFMT sessions in our study.

Although all women who participated in this trial experienced distress from their symptomatic prolapse, we showed that the effect of both treatments was lower than expected based on the results of other studies. Given that some women only experienced mild distress related to their pelvic floor symptoms, we might expect a larger effect for both pessary treatment and PFMT among women with bothersome symptoms and a wish for treatment. We therefore encourage that physicians adopt a proactive attitude to prolapse and that women with bothersome prolapse-related symptoms be informed about the available treatment options, but active screening for prolapse cannot be recommended. The results of our study showed that pessary treatment seems to be more effective in improving prolapse-specific symptoms than PFMT. Therefore, our advice would be to start with pessary treatment in women with mainly prolapse-specific symptoms. An advantage of pessary treatment is that it was associated with lower costs compared with PFMT. It should, however, also be taken into account that pessary fitting fails in a considerable portion of women and that pessary treatment was associated with more side effects compared with PFMT. For women with pelvic floor symptoms other than prolapse-specific symptoms, we are not able to pronounce a preference for pessary treatment or PFMT because there was no significant difference between PFMT and pessary treatment. Therefore, our advice would be to inform women about both treatments, including the advantages and disadvantages, to ensure that women are able to make an informed choice between both treatments.

CONCLUSIONS

This is the first study to investigate the effectiveness of pessary treatment and PFMT over a 2-year period in women aged 55 years or older with symptomatic prolapse at or beyond the hymen identified by screening. In this population, there was no significant difference between pessary treatment and PFMT in the reduction of pelvic floor symptoms, but women with typical prolapse symptoms seemed to benefit more from pessary treatment rather than from PFMT. Pessary treatment was preferable to PFMT in the cost-effectiveness analysis, with PFMT being more expensive but no more effective. When counseling women for prolapse treatment it should, however, be taken into account that pessary fitting fails in a considerable portion of women and that pessary treatment was associated with more side effects compared with PFMT.

Future research should continue down several avenues: we need to investigate the effectiveness of pessary treatment and PFMT in a primary care population of women with bothersome symptoms and a wish for treatment, and we should do research to identify the characteristics of women with the greatest potential for benefit from pessary treatment. Finally, it would be interesting to explore the effectiveness of the combination of PFMT and pessary treatment.

REFERENCES

1. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction.Neurourol Urodyn 2010;29:4-20.
2. Slieker-ten Hove MC, Pool-Goudzwaard AL, Eijkemans MJ, Steegers- Theunissen RP, Burger CW, Vierhout ME. The prevalence of pelvic organ prolapse symptoms and signs and their relation with bladder and bowel disorders in a general female population. Int Urogynecol J Pelvic Floor Dysfunct 2009;20:1037-1045.
3. Swift S, Woodman P, O'Boyle A, et al. Pelvic Organ Support Study (POSST): the distribution, clinical definition, and epidemiologic condition of pelvic organ support defects. Am J Obstet Gynecol 2005;192:795-806.
4. Jelovsek JE, Maher C, Barber MD. Pelvic organ prolapse. Lancet 2007;369:1027-1038.
5. Tok EC, Yasa O, Ertunc D, Savas A, Durukan H, Kanik A. The effect of pelvic organ prolapse on sexual function in a general cohort of women. J Sex Med 2010;7:3957-3962.
6. Fritel X, Varnoux N, Zins M, Breart G, Ringa V. Symptomatic pelvic organ prolapse at midlife, quality of life, and risk factors. Obstet Gynecol 2009;113:609-616.
7. Cheon C, Maher C. Economics of pelvic organ prolapse surgery. Int Urogynecol J 2013;24:1873-1876.
8. Wu JM, Kawasaki A, Hundley AF, Dieter AA, Myers ER, Sung VW. Predicting the number of women who will undergo incontinence and prolapse surgery, 2010 to 2050. Am J Obstet Gynecol 2011;205:230.e1-230.e5.
9. Cundiff GW, Weidner AC, Visco AG, Bump RC, Addison WA. A survey of pessary use by members of the American urogynecologic society. Obstet Gynecol 2000;95:931-935.
10. Barber MD, Walters MD, Cundiff GW; PESSRI Trial Group. Responsiveness of the Pelvic Floor Distress Inventory (PFDI) and Pelvic Floor Impact Questionnaire (PFIQ) in women undergoing vaginal surgery and pessary treatment for pelvic organ prolapse. Am J Obstet Gynecol 2006;194:1492-1498.
11. Clemons JL, Aguilar VC, Tillinghast TA, Jackson ND, Myers DL. Patient satisfaction and changes in prolapse and urinary symptoms in women who were fitted successfully with a pessary for pelvic organ prolapse. Am J Obstet Gynecol 2004;190:1025-1029.
12. Cundiff GW, Amundsen CL, Bent AE, et al. The PESSRI study: symptom relief outcomes of a randomized crossover trial of the ring and Gellhorn pessaries. Am J Obstet Gynecol 2007;196:405.e1-405.e8.
13. Fernando RJ, Thakar R, Sultan AH, Shah SM, Jones PW. Effect of vaginal pessaries on symptoms associated with pelvic organ prolapse. Obstet Gynecol 2006;108:93-99.
14. Patel M, Mellen C, O'Sullivan DM, LaSala CA. Impact of pessary use on prolapse symptoms, quality of life, and body image. Am J Obstet Gynecol 2010;202:499.e1-499.e4.

15. Kashyap R, Jain V, Singh A. Comparative effect of 2 packages of pelvic floor muscle training on the clinical course of stage I-III pelvic organ prolapse. Int J Gynaecol Obstet 2013;121:69-73.
16. Braekken IH, Majida M, Engh ME, Bo K. Can pelvic floor muscle training reverse pelvic organ prolapse and reduce prolapse symptoms? An assessor-blinded, randomized, controlled trial. Am J Obstet Gynecol 2010;203:170.e1-170.e7.
17. Ghroubi S, Kharrat O, Chaari M, Ben Ayed B, Guermazi M, Elleuch MH. Effect of conservative treatment in the management of low-degree urogenital prolapse. Ann Readapt Med Phys 2008;51:96-102.
18. Hagen S, Stark D, Glazener C, et al. Individualised pelvic floor muscle training in women with pelvic organ prolapse (POPPY): a multicentre randomised controlled trial. Lancet 2014;383:796-806.
19. Hagen S, Stark D, Glazener C, Sinclair L, Ramsay I. A randomized controlled trial of pelvic floor muscle training for stages I and II pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2009;20:45-51.
20. Piya-Anant M, Therasakvichya S, Leelaphatanadit C, Techatrisak K. Integrated health research program for the Thai elderly: prevalence of genital prolapse and effectiveness of pelvic floor exercise to prevent worsening of genital prolapse in elderly women. J Med Assoc Thai 2003;86:509-515.
21. Stupp L, Resende AP, Oliveira E, Castro RA, Girao MJ, Sartori MG. Pelvic floor muscle training for treatment of pelvic organ prolapse: an assessor-blinded randomized controlled trial. Int Urogynecol J 2011;22:1233-1239.
22. Wiegersma M, Panman CMCR, Kollen BJ, Berger MY, Lisman-Van Leeuwen Y, Dekker JH. Effect of pelvic floor muscle training compared with watchful waiting in older women with symptomatic mild pelvic organ prolapse: randomised controlled trial in primary care. BMJ 2014;349:g7378.
23. Bugge C, Adams EJ, Gopinath D, Reid F. Pessaries (mechanical devices) for pelvic organ prolapse in women. Cochrane Database Syst Rev 2013;2:CD004010.
24. Wiegersma M, Panman CMCR, Kollen BJ, et al. Pelvic floor muscle training versus watchful waiting or pessary treatment for pelvic organ prolapse (POPPS): design and participant baseline characteristics of two parallel pragmatic randomized controlled trials in primary care. Maturitas 2014;77:168-173.
25. Bump RC, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175:10-17.
26. Barber MD, Walters MD, Bump RC. Short forms of two conditionspecific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). Am J Obstet Gynecol 2005;193:103-113.
27. Utomo E, Blok BF, Steensma AB, Korfage IJ. Validation of the Pelvic Floor Distress Inventory (PFDI-20) and Pelvic Floor Impact Questionnaire (PFIQ-7) in a Dutch population. Int Urogynecol J 2014;25:531-544.

28. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-233.
29. Rogers RG, Coates KW, Kammerer-Doak D, Khalsa S, Qualls C. A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). Int Urogynecol J Pelvic Floor Dysfunct 2003;14:164-168.
30. Burgio KL, Goode PS, Richter HE, Locher JL, Roth DL. Global ratings of patient satisfaction and perceptions of improvement with treatment for urinary incontinence: validation of three global patient ratings. Neurourol Urodyn 2006;25:411-417.
31. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, Krol M, Severens H, Brouwer W. Manual iMTA Medical Cost Questionnaire (iMCQ). Rotterdam (The Netherlands): iMTA Erasmus University Rotterdam; 2013.
32. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-1108.
33. Messelink B, Benson T, Berghmans B, et al. Standardization of terminology of pelvic floor muscle function and dysfunction: report from the pelvic floor clinical assessment group of the International Continence Society. Neurourol Urodyn 2005;24:374-380.
34. Culligan PJ, Scherer J, Dyer K, et al. A randomized clinical trial comparing pelvic floor muscle training to a Pilates exercise program for improving pelvic muscle strength. Int Urogynecol J 2010;21:401-408.
35. Twisk JWR. Applied Multilevel Analysis. Practical Guides to Biostatistics and Epidemiology. Cambridge: Cambridge University Press; 2006.
36. Twisk JWR. Applied Longitudinal Data Analysis for Epidemiology. A Practical Guide. 4th ed. New York: Cambridge University Press; 2003.
37. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Guidelines for coststudies. Methods and unit prices for economic evaluations in health care. Dutch Health Care Insurance Board; Actualized version 2010.
38. Thakar R, Stanton S. Management of genital prolapse. BMJ 2002;324:1258-1262.
39. Gutman RE, Ford DE, Quiroz LH, Shippey SH, Handa VL. Is there a pelvic organ prolapse threshold that predicts pelvic floor symptoms? Am J Obstet Gynecol 2008;199:683.e1-683.e7.
40. Powers K, Lazarou G, Wang A, et al. Pessary use in advanced pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2006;17:160-164.
41. Clemons JL, Aguilar VC, Tillinghast TA, Jackson ND, Myers DL. Risk factors associated with an unsuccessful pessary fitting trial in women with pelvic organ prolapse. Am J Obstet Gynecol 2004;190:345-350.
42. Geoffrion R, Zhang T, Lee T, Cundiff GW. Clinical characteristics associated with unsuccessful pessary fitting outcomes. Female Pelvic Med Reconstr Surg 2013;19:339-345.
43. Handa VL, Jones M. Do pessaries prevent the progression of pelvic organ prolapse? Int Urogynecol J Pelvic Floor Dysfunct 2002;13:349-351.
44. Hanson LA, Schulz JA, Flood CG, Cooley B, Tam F. Vaginal pessaries in managing women with

pelvic organ prolapse and urinary incontinence: patient characteristics and factors contributing to success. Int Urogynecol J Pelvic Floor Dysfunct 2006;17:155-159.

45. Lewthwaite BJ, Staley D, Girouard L, Maslow K. Characteristics of women with continued use of vaginal pessaries. Urol Nurs 2013;33:171-176.
46. Maito JM, Quam ZA, Craig E, Danner KA, Rogers RG. Predictors of successful pessary fitting and continued use in a nurse-midwifery pessary clinic. J Midwifery Womens Health 2006;51:78-84.
47. Manchana T. Ring pessary for all pelvic organ prolapse. Arch Gynecol Obstet 2011;284:391-395.
48. Markle D, Skoczylas L, Goldsmith C, Noblett K. Patient characteristics associated with a successful pessary fitting. Female Pelvic Med Reconstr Surg 2011;17:249-252.
49. Mutone MF, Terry C, Hale DS, Benson JT. Factors which influence the short-term success of pessary management of pelvic organ prolapse. Am J Obstet Gynecol 2005;193:89-94.
50. Nguyen JN, Jones CR. Pessary treatment of pelvic relaxation: factors affecting successful fitting and continued use. J Wound Ostomy Continence Nurs 2005;32:255-261.
51. Hullfish KL, Trowbridge ER, Stukenborg GJ. Treatment strategies for pelvic organ prolapse: a cost-effectiveness analysis. Int Urogynecol J 2011;22:507-515.

APPENDIX I PFMT LIFESTYLE AND TOILET ADVICE AND EXERCISE PROGRAM

Lifestyle advices

- Avoid heavy lifting.
- Avoid constipation: drink at least 1.5-2 liters of fluids daily and eat plenty of fiber (whole meal products, vegetables, fruit). Ask your general practitioner for a laxative if this is not sufficient.
- Use the Knack exercise before and during any increases abdominal pressure.
- If smoking: try to stop.
- If overweight: try to lose weight.

Toilet instructions

- Keep your feet flat on the floor.
- Micturition: sit up straight (concave back), relax your pelvic floor, do not strain.
- Defecation: go to the toilet if you feel the urge to defecate, sit down with a convex back, relax your pelvic floor and take your time. If necessary, strain slightly but keep breathing.

Basic exercises program

- Perform 3 series of 8-12 fast contractions of 1 second followed by 1 second of relaxation. Take 30-60 seconds of rest between series.
- Perform 3 series of 8-12 contractions of 6-10 seconds followed by 6-10 seconds of relaxation. Take 1-2 minutes of rest between series.
- Perform a (nearly) maximal contraction and hold this for 6-10 seconds, try to make 3-5 fast contractions of 1 second on top of the maximal contraction. Repeat this exercise 3 times and take 1-2 minutes of rest between exercises.*

Examples of additional exercises*

- Perform a step wise contraction: start at 30%, followed by 60%, up to 100% and also perform a stepwise relaxation: from 100% to 60% to 30% to complete relaxation. Repeat this exercise 3 times and take 1-2 minutes of rest between exercises.
- To focus on the ventral part of the pelvic floor: perform your basic exercises while sitting on a chair with a concave back and your feet positioned on the floor with your toes pointing inwards.
- To focus on the dorsal part of the pelvic floor: perform your basic exercises while sitting on a chair with a convex back and your feet positioned on the floor with your toes pointing outwards.
- Perform a contraction starting at the dorsal part of the pelvic floor, moving to the ventral part of the pelvic floor (like 'closing a zipper'). Repeat this exercise 3 times and take 1-2 minutes of rest between exercises.

*Not in participants with an overactive pelvic floor